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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,766	07/22/2005	Gerhard Hoefle	930008-2193	2943

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EXAMINER	
KOSACK, JOSEPH R	

ART UNIT	PAPER NUMBER
1626	

MAIL DATE	DELIVERY MODE
11/01/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/520,766	HOEFLE, GERHARD	
	Examiner	Art Unit	
	Joseph Kosack	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 9-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-19 are pending in the instant application.

Amendments

The amendment filed on August 9, 2007 has been acknowledged and has been entered into the application file.

Previous Claim Objections

Claims 1-7 and 9-10 were previously objected to for containing elected and non-elected subject matter. Applicant has cancelled the non-elected subject matter from the claims, and the objection is withdrawn.

Previous Claim Rejections - 35 USC § 101

Claim 10 was previously rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. The claim has been rewritten as a method claim, and the rejection is withdrawn.

Previous Claim Rejections - 35 USC § 112

Claim 10 was previously rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating some cancers, does not reasonably provide enablement for treating all cancers.

Applicant has traversed the rejection on the grounds that epothilones are active against a number of cancers, are in clinical trials for the treatment of those cancers and that the compounds have similar properties to paclitaxel.

This is not found to be persuasive. Firstly, paclitaxel is only for use in ovarian cancer, breast cancer, non-small cell lung cancer, and AIDS-related Kaiposi's sarcoma. See TAXOL drug insert, March 2003, page 6, column 2. While Flörsheimer et al. show that epothilones have activity on some cancer lines that paclitaxel does not, the types of cancer tested are only a small sample of the many various cancers that are claimed by the Applicant. There has not been any one compound, not even paclitaxel, that has been shown to be able to treat each and every cancer. In unpredictable arts such as cancer treatment, increased *in vitro* and *in vivo* evidence is required in order to show enablement for a claim as broad as that to treat any type of cancer. Applicant has shown enablement support for certain cancers, but not for all cancers. Therefore, at this time, the rejection must be maintained.

Claim 10 was previously rejected under 35 U.S.C. 112, second paragraph, as being drawn to an indefinite use claim. The claim has been rewritten as a method claim, and the rejection is withdrawn.

Previous Claim Rejections - 35 USC § 102

Claims 1-4, 6-7, and 9-10 were previously rejected under 35 U.S.C. 102(b) as being anticipated by Vite et al. (WO 99/02514 A2).

Applicant has traversed the rejection on the grounds that the Examiner presented and ad hoc collection of elements.

Applicant is reminded that a species anticipates a genus. The Examiner pointed to a particular species that reads on the instant claims. In Markush practice, once one of the alternate possibilities is anticipated, the entire claim is rejected for anticipation.

Applicant has not cancelled the anticipated subject matter, and the rejection is maintained.

Previous Claim Rejections - 35 USC § 103 and ODP

Claims 1-7 and 9-10 were previously rejected under 35 U.S.C. 103(a) as being unpatentable over Vite et al. (WO 99/02514 A2) in view of Patani et al. (*Chemical Reviews, 1996*, 3147-3176).

Applicant has traversed the rejection on the grounds that Patani et al. teaches away from making the replacement.

This is not found to be persuasive since the quote that Applicant relies on from Patani is drawn from modifying a normal substrate of an enzyme to yield an inhibitor where as in the instant case, a macrocycle which is not a natural human enzyme substrate is modified by the change proposed by the Examiner. Therefore, Patani et al. does not actually teach away from making the change and the rejection is maintained.

Claims 1-4, 6-7, and 9 rejected under 35 U.S.C. 103(a) as being unpatentable over Hoefle (USPN 6,288,237).

Applicant has traversed the rejection on the grounds that there is no motivation to make the change and that methyl has more steric bulk than hydrogen. This is not found to be persuasive because while methyl may have more steric bulk than hydrogen, they have been shown in the courts consistently to be obvious variants in the absence of evidence to the contrary. Additionally, with the large size of the ring, unless the R_3 position is critical to the activity of the molecule, changing the substitution would be expected to yield a compound of the same utility and comparable activity. The rejection

is maintained. As the obviousness double patenting rejection of claims 1-4, 6-7, and 9 is traversed on the same grounds, that rejection is also maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-14 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating some cancers, does not reasonably provide enablement for treating all cancers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The Nature of the Invention

The nature of the invention is the treatment of all cancers (Claims 11). Specifically, solid tumors of any type of cancer (claim 12), multi-drug resistant cancer of any type (claim 13), and leukemia (claim 14) are claimed.

The State of the Prior Art and the Predictability or Lack Thereof in the Art

The state of the prior art is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The instant claimed invention is highly unpredictable as discussed below:
It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

Nicolaou et al. (*Angew. Chem. Int. Ed. 1998*, 2014-2045) teach that epithilones A-E along with structural analogs synthesized by the group are effective in inhibiting ovarian and breast cancer cell lines (Table 7, page 2041). Nicolaou et al. do not teach any testing or effectiveness of analogs of epithilones A or B with other types of cancer cell lines.

Flörsheimer et al. (*Expert Opin. Ther. Patents 2001*, 951-968) teach that it is too early to judge whether or not epothilone-based agents will one day be clinically useful anti-cancer drugs (page 965, column 2, last paragraph). Flörsheimer et al. do teach though that naturally occurring epothilones are effective in inhibiting net growth of certain human cancer lines (page 952, Table 1).

Hence, in the absence of a showing of correlation between all cancers claimed as capable of treatment by the claimed compounds, one of skill in the art is unable to fully predict possible results from the administration of the compound of formula 1 due to the unpredictability of the role of those compounds in treating all cancers, and the unpredictability of the ability of the compound of formula 1 to cause toxicity or any improvement in condition.

The Amount of Direction or Guidance Present and the Presence or Absence of Working Examples

The specification does not show any in vitro or in vivo data of the compounds. The specification directs the person of ordinary skill in the art to consult the two references cited in the previous section for guidance in the treatment of all cancers.

The Breadth of the Claims

The breadth of the claims is the treatment of all cancers (Claims 11). Specifically, solid tumors of any type of cancer (claim 12), multi-drug resistant cancer of any type (claim 13), and leukemia (claim 14) are claimed.

The Quantity of Experimentation Needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine which cancers can be treated with the compounds of the instant invention, dosages, the method of drug delivery, and any potential combination therapies.

The Level of Skill in the Art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of formula 1 for the treatment of all cancers. As a result, necessitating one of skill to perform an exhaustive search for which cancers can be treated by what compounds of formula 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to

engage in undue experimentation to test which diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

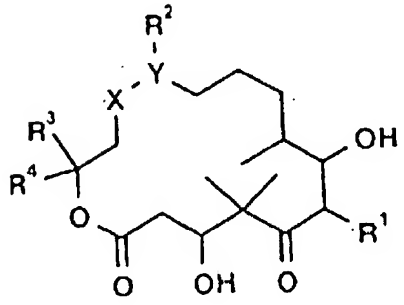
Claim Rejections - 35 USC § 102

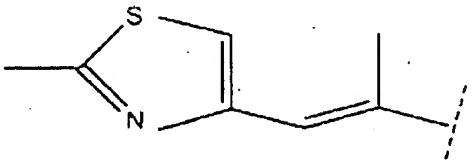
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6-7, and 9-19 rejected under 35 U.S.C. 102(b) as being anticipated by Vite et al. (WO 99/02514 A2).

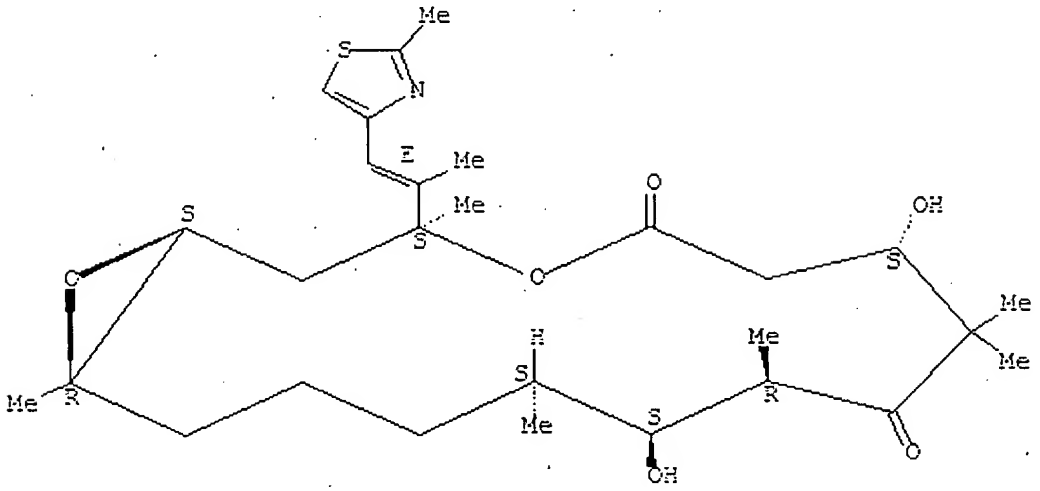
The instant application sites compounds of formula 1:



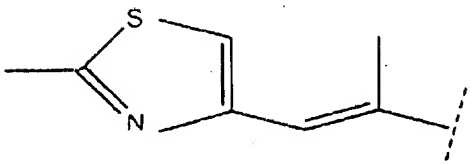
where R^4 is 

and all other substituents are as defined as well as the use of the compounds for treating cancer.

Vite et al. teach a compound of the formula:



which reads on the claims where R^1, R^2, and R^3 are methyl, R^4 is



, and X-Y is epoxide. See page 44, lines 33-35. Vite et al. also teach a method of using the compounds to treat various cancers. See page 8-9.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

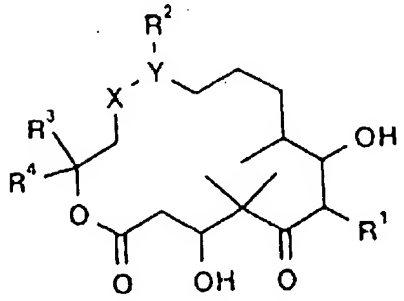
> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

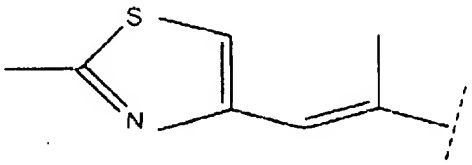
The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-7 and 9-19 rejected under 35 U.S.C. 103(a) as being unpatentable over Vite et al. (WO 99/02514 A2) in view of Patani et al. (*Chemical Reviews, 1996*, 3147-3176).

The instant application sites compounds of formula 1:

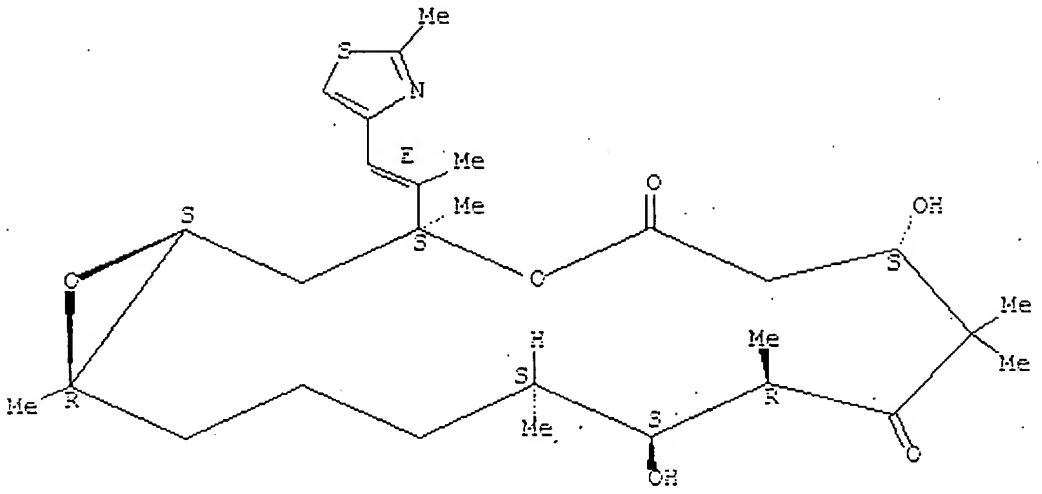


where R^4 is 

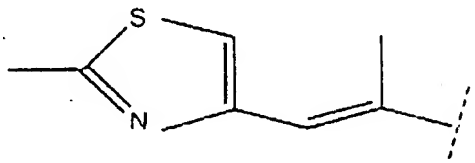
, R^3 is trifluoromethyl, and all other substituents are as defined as well as the use of the compounds for treating cancer.

Determination of the scope and content of the prior art (MPEP §2141.01)

Vite et al. teach a compound of the formula:



where R^1,



R^2, and R^3 are methyl, R^4 is , and X-Y is epoxide. See page 44, lines 33-35. Vite et al. also teach a method of using the compounds to treat various cancers. See page 8-9.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Vite et al. do not teach a trifluoromethyl group in place of a methyl group at the R^3 position.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

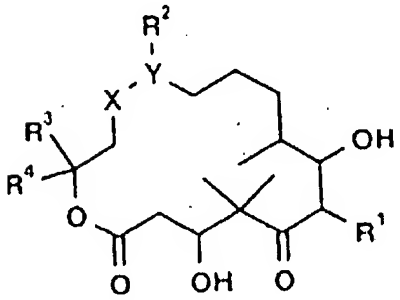
Patani et al. teach the general bioisosteric replacement of fluorine for hydrogen to yield new pharmaceuticals with similar utility and comparable, if not increase, activity. See pages 3149-3150.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to take the known epothilone of Vite et al. and replace the hydrogens of the R^3 methyl group for fluorine according to Patani et al. and make the claimed invention with a reasonable expectation of success. The motivation to do so is provided by Patani et al. Patani et al. teach that bioisosterism represents one approach used by the medicinal chemist for the rational modification of lead compounds into safer and more clinically effective agents. See page 3147.

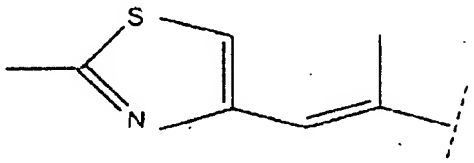
Thus, the claimed invention as a whole was *prima facie* obviousness over the combined teachings of the prior art.

Claims 1-4, 6-7, and 9 rejected under 35 U.S.C. 103(a) as being unpatentable over Hoefle (USPN 6,288,237).

The instant application sites compounds of formula 1:

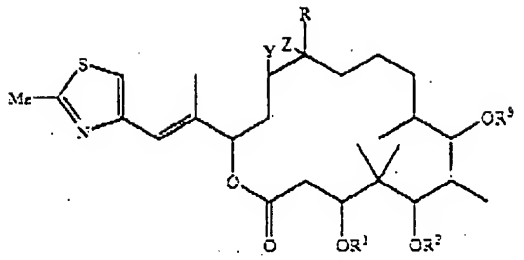


where R^4 is



and all other substituents are as defined.

Determination of the scope and content of the prior art (MPEP §2141.01)



Hoefle teaches compounds of the formula:

where R can be hydrogen or C_{1-4} alkyl, R^1-R^3 can be hydrogen, and Y-Z can be epoxide of C=C. See column 14, lines 15-38.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Hoefle does not teach the R^3 group of the instant application which can be methyl.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

Hydrogen and methyl are deemed obvious variants. In re Wood, 199 USPQ 137

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to take the known epothilone of Hoefle and replace the hydrogen in the R^3 position for methyl and make the claimed invention with a reasonable expectation of success. The motivation to do so is that obvious variants have similar activity and similar utility.

Thus, the claimed invention as a whole was *prima facie* obviousness over the combined teachings of the prior art.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

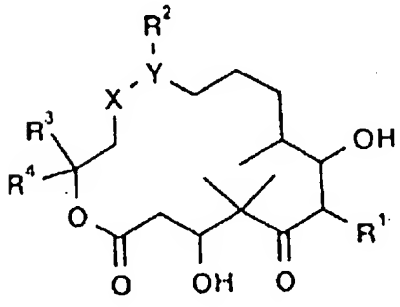
and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

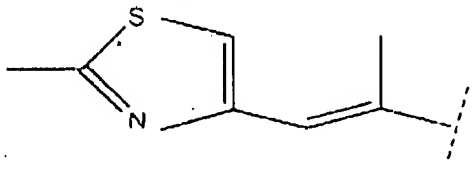
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 6-7, and 9 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,288,237. Although the conflicting claims are not identical, they are not patentably distinct from each other because they teach the same art specific subject matter.

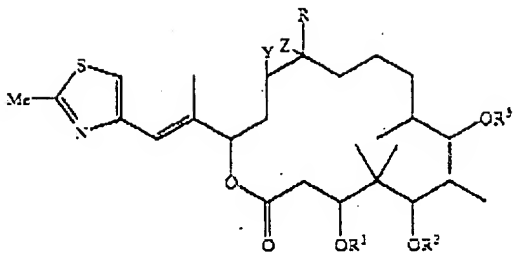
The instant application sites compounds of formula 1:



where R^4 is



and all other substituents are as defined.



'237 teaches compounds of the formula:

where R can be hydrogen or C_{1-4} alkyl, R^1-R^3 can be hydrogen, and Y-Z can be epoxide of C=C.

'237 does not teach the R^3 group of the instant application which can be methyl. Hydrogen and methyl are deemed obvious variants. In re Wood, 199 USPQ 137

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to take the known epothilone of '237 and replace the hydrogen in the R^3 position for methyl and make the claimed invention with a reasonable expectation of success. The motivation to do so is that obvious variants have similar activity and similar utility.

Conclusion

Claims 1-7 and 9-19 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Kosack whose telephone number is (571)-272-5575. The examiner can normally be reached on M-F 6:30 A.M. until 4:00 P.M. The examiner has every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Joseph R Kosack

Joseph Kosack
Patent Examiner
Art Unit 1626

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